REMARKS

Claims 2-4, 8, 9, 13-17, 19, 33-36, and 38-44 are pending. Claims 2-4, 8, 9, 13-17, 19, and 33-36 have been rejected. Claims 33, 38, and 41 have been amended. The allowance of Claims 38-44 is noted with appreciation. Reconsideration of Claims 2-4, 8, 9, 13-17, 19, and 33-36, and allowance of Claims 2-4, 8, 9, 13-17, 19, 33-36, and 38-44 is respectfully requested.

The Claimed Invention: Independent Claim 33

Claim 33 is the pending independent claim that stands rejected. Claims 2-4, 8, 9, 13-17, 19, and 34-36 depend from Claim 33.

Claim 33 recites a composition that includes a hydrophilic conjugate. The hydrophilic conjugate has three components: (1) a hydrophobic component linked to (2) a hydrophilic component by (3) a pH-sensitive linkage. Claim 33 also recites two additional features: (a) the pH-sensitive linkage is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component; and (b) the hydrophobic component is membrane-disruptive and allows enhanced transport through a membrane only when released from the hydrophilic conjugate. Therefore, at a pH less than 6.5, the conjugate's pH-sensitive linkage cleaves releasing the hydrophobic component from the hydrophilic component. When released from the hydrophilic component, the hydrophobic component becomes membrane disruptive thereby allowing for transport through the membrane. When the conjugate further includes a therapeutic or diagnostic agent, release of the hydrophobic component by pH-sensitive linkage cleavage allows for the released hydrophobic component, which is now membrane disruptive, to disrupt the membrane thereby allowing delivery of the therapeutic or diagnostic agent through the disrupted membrane. See FIGURES 3 and 4 of the application as filed.

The cited references, either alone or in any combination, fail to describe, suggest, or provide any motivation to make the conjugate having the three components recited in Claim 33.

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The Rejection of Claims 2-4, 8-10, 13-15, 19, and 33-35 Under 35 U.S.C. § 102(e)

The Examiner's Action states that Claims 2-4, 8-10, 13-15, and 33-35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,210,717, issued to Choi et al. Applicants believe that the rejection pertains to Claims 2-4, 8, 9, 13-15, 19, and 33-35. Withdrawal of the rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8, 9, 13-15, and 33-35 depend. As noted above, Claim 33 relates to a hydrophilic conjugate having three components: (1) a hydrophobic component, which is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate, linked to (2) a hydrophilic component by (3) a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component.

The Examiner states that the Choi reference describes a graft copolymer comprising a hydrophobic polyester portion and a hydrophilic cation portion having a pH-sensitive linkage (i.e., an ester bond) between the hydrophobic portion and the hydrophilic portion. To support the statement, the Examiner cites column 2, lines 40-55 and column 6, lines 45-57. Applicants respectfully disagree with the Examiner's reading of the Choi reference. Applicants' submit the Choi reference fails describe a copolymer having a hydrophobic portion covalently coupled to a hydrophilic portion through an ester bond.

Column 2 of the Choi Reference. At column 2, lines 40-55, the Choi reference describes the polyester polycation copolymer. At column 2, lines 37-41, the reference states that the

> polyester polycation copolymer can be either a diblock copolymer comprising a hydrophobic polyester block bonded to a hydrophilic polycation block by an amide linkage or a graft copolymer comprising a hydrophobic polyester portion and a hydrophilic cation portion. (Emphasis added.)

At column 2, lines 42-49, the reference describes the polyester of the copolymer. At column 2, lines 49-55, the reference describes the polycation. Nowhere does the reference state

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that the hydrophilic block or portion is bonded to the hydrophobic block or portion through an ester linkage. In fact, as noted in applicants' previous response, the reference specifically states that the diblock copolymer comprises a "hydrophobic polyester block bonded to a hydrophilic polycation block by an amide linkage."

Column 2 of the reference fails to describe or suggest a copolymer having an ester linkage to bond the hydrophobic block or portion to the hydrophilic block or portion.

Column 6 of the Choi Reference. At column 6, lines 45-57, the Choi reference describes the preparation of the polyester-polycation block or graft copolymer, and identifies several polyester segments (see lines 47-52) and several polycation segments (see lines 52-57). Regarding the polycation segment, the reference states that "[t]he polycation segment is preferably a polycation wherein the monomer units are connected by an ester or amide linkage." Although the reference states that the monomer of the polycation segment can be connected by an ester linkage, the reference in no way states or suggests that the polyester segment is connected to the polycation segment by an ester linkage.

Column 6 of the reference fails to describe or suggest a copolymer having an ester linkage to bond the hydrophobic block or portion to the hydrophilic block or portion.

Applicants refer the Examiner to Examples 1 and 3, which describe the preparation of representative polyester-polycation copolymers.

Example 1 describes the preparation of poly(L-lactic acid)-poly(L-serine ester) diblock copolymer by reacting an amine-terminated poly(L-lactic acid) with poly(N-benzyloxycarbonyl-L-serine ester) using dicyclohexylcarbodiimide. The product is an amide-linked polyester-polycation copolymer.

Example 3 describes the preparation of poly(L-lactic acid)-poly(L-lysine) graft copolymer by activating the carboxyl end group of poly(L-lactic acid) with

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isobutylchloroformate (to provide an amine-reactive acid chloride) followed by reaction with poly(L-lysine) through its amino group to provide an amide-linked polyester-polycation copolymer.

Applicants' respectfully submit that the Choi references fails to describe or suggest the use of an ester group to link a polyester (hydrophobic) block or segment to a polycation (hydrophilic) block or segment to provide either a diblock or graft copolymer having polyester linked to polycation through an ester group.

Because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-15, 19, and 33-35 Under 35 U.S.C. § 102(e)/103(a)

The Examiner's Action states that Claims 2-4, 8-10, 13-15, 19, and 33-35 stand rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 6,210,717, issued to Choi et al. Applicants believe that the rejection pertains to Claims 2-4, 8, 9, 13-15, 19, and 33-35. Withdrawal of the rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8, 9, 13-15, 19, and 33-35 depend.

For the reasons noted above, because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

Furthermore, applicants submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. The Choi polymers do not include a pH-sensitive linkage that, at pH less than 6.5, cleaves and releases a membrane-disruptive hydrophobic component thereby affecting membrane disruption and drug

delivery. The Choi polymers include an amide link that joins a hydrophobic block or segment to a hydrophilic block or segment. First, the amide link will not be cleaved at a pH less than 6.5, as recited in the claimed invention. Moreover, these polymers are not designed to cleave at the amide link to release the polymer blocks. For the Choi polymers, drug (gene) delivery does not involve cleavage of the amide link. In contrast, hydrolysis of the pH-sensitive linkage at a pH less than 6.5 in the claimed invention releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug (when the conjugate of the invention further include a drug).

The cited reference fails to suggest the claimed invention because the cited reference fails to teach or suggest a pH-sensitive linkage. The cited reference provides for drug delivery without bond cleavage of any kind. The claimed invention provides for drug delivery by simple acid hydrolysis of a chemically labile linkage that is pH-sensitive in the environment of the endosome. One skilled in the art would not be motivated by the teaching of the Choi reference to modify the amide-linked diblock copolymer to arrive at the pH-sensitive linked conjugate of the claimed invention.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable of the cited reference. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-16, 19, and 33-36 Under 35 U.S.C. § 102(e)

Claims 2-4, 8-10, 13-16, 19, and 33-36 stand rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,939,453, issued to Heller et al. Applicants believe that the rejection pertains to Claims 2-4, 8, 9, 13-16, 19, and 33-36. Withdrawal of the rejection is respectfully requested for the following reasons.

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Claim 33 is the independent claim from which Claims 2-4, 8, 9, 13-16, 19, and 33-36 depend. As noted above, Claim 33 relates to a hydrophilic conjugate having three components: (1) a hydrophobic component, which is membrane-disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic conjugate, linked to (2) a hydrophilic component by (3) a pH-sensitive linkage that is stable at a pH between 6.8 and 8 and hydrolyzed at a pH less than 6.5 to release the hydrophobic component.

The Heller reference describes block copolymers that include hydrophobic and hydrophilic blocks. These polymers form bioerodible matrices for the sustained release of active agents. The copolymers are polyethylene glycol (PEG)/poly(orthoester) (POE) block copolymers.

The Examiner states that the Heller copolymers include acetal linkages. Applicants respectfully disagree. None of the Heller block copolymers include an acetal group (i.e., two different oxygen groups attached to a single carbon). Rather, these block copolymers include orthoester groups (i.e., three different oxygen groups attached to a single carbon). See Formulas I-III, where A is OR_4 or OR_5.

The Heller copolymers are bioerodible (i.e., biodegradable) polymers. In contrast to the claimed invention, the block copolymers described in the Heller reference do not include a hydrophobic component linked to a hydrophilic component by a pH-sensitive linkage. More particularly, the block copolymers described in the reference do not include a hydrophobic component that is released from the hydrophilic conjugate by cleavage of the pH-sensitive linkage. Although the block copolymers described by the reference are bioerodible, these polymers do not yield a hydrophobic component that is membrane disruptive. At Col. 5, lines 9-16, the reference states that bioerosion occurs by hydrolysis of linkages between and within the poly(orthoester) block. Thus, bioerosion (biodegradation) occurs through hydrolysis within the

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hydrophobic block and does not result in the release of a hydrophobic component that is membrane disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic component (PEG).

Cleavage of the orthoester link between the PEG block and the POE block does release the PEG block. However, because the POE block consists of orthoester linkages, the POE block is further hydrolyzed under the same conditions that effects hydrolysis of the orthoester link joining the blocks, and that further hydrolysis of the POE block provides only simple esters and a $C_5H_{12}O_4$ tetra-ol, neither of which is "a hydrophobic component that is membrane-disruptive and allows enhanced transport through a membrane," as in the claimed invention.

Because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 2-4, 8-10, 13-16, 19, and 33-36 Under 35 U.S.C. § 102(e)/103(a)

Claims 2-4, 8-10, 13-16, 19, and 33-36 stand rejected under 35 U.S.C. § 102(e) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,939,453, issued to Heller et al. Applicants believe that the rejection pertains to Claims 2-4, 8, 9, 13-16, 19, and 33-36. Withdrawal of the rejection is respectfully requested for the following reasons.

Claim 33 is the independent claim from which Claims 2-4, 8, 9, 13-16, 19, and 33-36 depend.

For the reasons noted above, because the cited reference fails to exactly describe the claimed invention, the reference is not anticipatory. Withdrawal of the rejection is respectfully requested.

Furthermore, applicants submit that the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention. The Heller

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polymers do not include a pH-sensitive linkage that, at pH less than 6.5, cleaves and releases a membrane-disruptive hydrophobic component thereby affecting membrane disruption and drug delivery. First, although the Heller polymers are bioerodible and biodegradable, the bioerosion or biodegradation results from hydrolysis of linkages between and within the poly(orthoester) block. This bioerosion and biodegradation occurs through hydrolysis within the hydrophobic block and does not result in the release of a hydrophobic component (POE) that is membrane disruptive and allows enhanced transport through a cellular membrane only when released from the hydrophilic component (PEG). Second, these polymers are not designed to cleave to release the polymer blocks, and more particularly, not to release a hydrophobic component that is membrane disruptive to effect drug delivery. The Heller polymers are designed to erode over time to provide slow release of materials associated with the polymers. In contrast, hydrolysis of the pH-sensitive linkage at a pH less than 6.5 in the claimed invention releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug (when the conjugate of the invention further include a drug).

The cited reference fails to suggest the claimed invention because the cited reference fails to teach or suggest a pH-sensitive linkage that, when cleaved, releases a membrane-disruptive hydrophobic component that disrupts the membrane thereby delivering the drug. One skilled in the art would not be motivated by the teaching of the Heller reference to modify the PEG-POE block copolymer to arrive at the conjugate of the invention having a hydrophilic component (that is membrane disruptive when cleaved from the conjugate) linked to a hydrophilic component by pH-sensitive linkage that is hydrolyzed at a pH less than 6.5.

Because the cited reference fails to teach, suggest, provide any motivation to make, or otherwise render obvious the claimed invention, the claimed invention is nonobvious and patentable of the cited reference. Withdrawal of the rejection is respectfully requested.

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Conclusion

In view of the above amendments and foregoing remarks, applicants believe that Claims 2-4, 8, 9, 13-17, 19, 33-36, and 38-44 are in condition for allowance. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1755.

Respectfully submitted,

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